Alcohol and the Skeletal System

As long ago as ancient Egypt, alcohol abuse was observed to confer a high risk for skeletal fracture (Conn 1985; Mathew 1992; Seller 1985). While an association between alcoholism and accidental injury is well recognized (Lucas 1987), there is evidence to suggest that alcoholics may also suffer from a generalized skeletal fragility that makes their bones more liable to fracture. Basic science studies have identified processes that shape bone that are disrupted by alcohol.

Even more provocative, some recent studies find that moderate intake of alcohol may actually protect against the loss of bone mass that characterizes the disease osteoporosis. Despite the difficulty of establishing with certainty how and to what extent alcohol affects bone and the risk of fracture, this issue is an important one for public health. At some time in their lives, 30 to 50 percent of U.S. women and 10 to 25 percent of U.S. men will suffer an osteoporosis-related fracture (Melton and Riggs 1983). Approximately one in five people will die within 6 months after suffering a hip fracture, and many more will become disabled and will not be able to return to their previous lifestyle (Avioli 1991).

Research Challenges

The study of the effects of alcohol on bone disease is complex for several reasons. First, it is extremely difficult to define and accurately quantify lifetime alcohol exposure, a problem compounded further when studying elderly individuals with impaired recall. Second, studies may obscure the immediate and delayed effects of alcohol, which can be markedly different. Third, individuals vary in many ways other than alcohol consumption that can affect their health. Confounding factors such as diet, exercise, smoking, and overall health must be taken into account in analyses.

Finally, any association (either positive or negative) between drinking and fracture rates is difficult to demonstrate because fractures are relatively uncommon events. Fracture incidence peaks at 3 to 4 percent per year in women over 75 years of age, while in younger women the incidence can be as low as 0.02 percent to 0.1 percent per year depending on the age group studied. Sample sizes (the number of people in the study) must be large to convincingly demonstrate an effect. Attention to these and other serious methodological issues is lacking in most published studies and may result in a distorted estimation of the true consequences of alcohol on the skeleton. Even when these factors are accounted for, current studies document associations but do not prove causality.

The majority of available data on the impact of social drinking on skeletal integrity comes from "case-control studies" and "cohort studies" designed to identify general risk factors for osteoporotic fractures, not to explore specifically the effect of alcohol consumption on fracture prevalence. In case-control studies, researchers identify individuals with a particular characteristic or condition they wish to study, such as past fractures. They then match these individuals with others without fractures and compare other features in their health history, such as alcohol use, to detect any pattern linking fracture risk to alcohol consumption. Cohort studies focus on a cohort or population not selected for any particular disease or condition, and either look back at that population's health history (retrospective studies) or follow them through a time period and measure the frequency of events such as fractures (prospective studies). However, to demonstrate that a particular health practice is beneficial, a randomized intervention study—in which similar numbers of participants are randomly assigned to a health intervention or to no such intervention, and the long-term outcome

is compared—is usually required to prove a cause-and-effect relationship. A study of the relationship between (moderate) alcohol intake and fracture risk would be a formidable undertaking, but would be likely to have important public health implications, considering the prevalence of osteoporosis and the prominence of drinking in the United States.

Alcohol-Induced Fractures

Modern-day scientific research on fracture prevalence in alcoholic subjects is based for the most part on small, inadequately controlled studies composed mostly of men, perhaps reflecting the more modest levels of alcohol consumption by women. While men hospitalized for alcohol-related problems are four times more likely to have experienced a rib fracture than similar individuals with no drinking problems (Lindsell et al. 1982) and up to 14 times more likely to exhibit spinal crush fractures (Crilly et al. 1988; Israel et al. 1980), the effect of more moderate alcohol consumption on the bones of healthy men and women has not been well explored. Evidence from epidemiologic studies is inconsistent, with some reporting a positive association between alcohol intake and fracture occurrence, and others detecting no such association.

A prospective, population-based study of 3,140 perimenopausal women found alcohol intake to be higher among women who experienced fractures during the study than among those without fractures (Tuppurainen et al. 1995). Among women who drank alcohol, the risk of a fracture was increased about 50 percent over the risk among women who did not drink. In another study, osteoporotic fracture risk was higher with increased weekly alcohol intake in postmenopausal women (Paganini-Hill et al. 1981). In this study, women drinking more than eight standard drinks per week were almost twice as likely as nondrinkers to have an osteoporotic fracture. (A standard drink is defined as 0.5 ounces [oz] or approximately 15 grams of pure alcohol consumed as either 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof distilled spirits.) A survey of 84,500 U.S. women between the ages of 34 and 59 found that daily consumption of 25 grams of alcohol (one to two drinks) was associated with a 133-percent increase in risk for hip fractures and a 38-percent increase for wrist fractures (Hernandez-Avila et al. 1991). Although osteoporotic fractures are generally less common in nonwhite women, consumption of seven or more standard drinks per week was associated with a twofold increased risk of hip fracture in a cohort study of Japanese women (Fujiwara et al. 1997) and a 4.6-fold increased risk in a case-control study of black women (Grisso et al. 1994).

In the Framingham Heart Study, for those younger than age 65, both moderate (two to six drinks per week) and heavy (more than seven drinks per week) current drinking substantially and significantly increased the risk of fracture compared with the risk of fracture associated with light drinking (less than two drinks per week). For example, male heavy drinkers younger than age 65 experienced almost 10 times the risk of hip fracture as men who drank lightly (Felson et al. 1988).

In contrast, other studies of similar size and design have not identified any significant association between alcohol intake and fracture risk. Two separate case-control studies of risk factors for hip fracture in women—one in Europe (Johnell et al. 1995) and the other in Australia (Cumming and Klineberg 1994)—found no significant effect of alcohol intake. Similarly, a prospective cohort study of 2,513 women who participated in the first National Health and Nutrition Examination Survey found that self-reported alcohol use was not related to subsequent hip fracture (Huang et al. 1996). Finally, no association was detected between frequency of alcohol intake and either vertebral deformity in a population-based survey of over 14,000 participants in Europe (Naves Diaz et al. 1997) or distal forearm fracture in a case-control study in the United Kingdom (O'Neill et al. 1996).

Thus considerable—though not unanimous—evidence suggests that excessive alcohol intake increases the risk of fracture. Further, the

consequences of smaller amounts of alcohol consumption on the skeletal integrity are not clear. Because of the much larger number of people at risk from moderate alcohol consumption, it is crucial that the impact of social drinking on skeletal integrity be better assessed.

Alcohol-Induced Osteopenia

Epidemiologic studies that find a relationship between alcohol and fracture risk do not reveal to what extent the increase is due to a greater risk of trauma. Alcohol intoxication creates conditions that favor accidents and falls, facilitating bone fractures (Lucas 1987). In a study comparing the blood alcohol concentration (BAC) (see the box "The ABC's of BAC's" in the chapter on prevention) of people who had had falls (and had come to a hospital emergency room) with that of pedestrians identified for comparison, the risk of falling was tripled in those with a BAC of 0.1 to 0.15 percent and 60 times higher in those with a BAC of 0.16 percent or higher, compared with people whose BAC was 0.1 percent or lower (Honkanen et al. 1983). In addition to the effects of intoxication, the impaired muscle control that can accompany withdrawal seizures, hypoglycemic (low blood sugar) attacks, and alcohol-associated neuromuscular disabilities probably also contributes to the increased fall frequency.

Beyond the risk of falls, however, emerging evidence suggests that alcoholics may also suffer from a generalized skeletal fragility that makes their bones more liable to fractures. Bone density is an important determinant of bone strength and is a predictor of fractures. As measures of bone strength are neither well defined nor clinically available, osteoporosis, for all practical purposes, is currently synonymous with low bone density (or osteopenia). Saville (1965) was the first to demonstrate the association of osteopenia with alcohol abuse. Using postmortem material from 198 cadavers, he observed that fat-free bone mass was markedly reduced in the 39 samples from individuals with a history of alcoholism. He noted that the bone mass of young alcoholic males was comparable to that of elderly, postmenopausal females.

Subsequent studies over the past quarter century have clearly demonstrated clinically relevant reductions in bone mass in alcoholics, especially in the heel bone, vertebral column, and hip (Peris et al. 1995; Spencer et al. 1986). In a recent prospective case-control analysis of risk factors for the development of osteoporosis, average alcohol consumption was two to three times higher in both osteoporotic males and osteoporotic females than in age-matched controls (Blaauw et al. 1994). In another study, premenopausal women who consumed more than two standard drinks per day exhibited 13 percent lower bone density of the hip compared with women who consumed less than one standard drink per week (Gonzalez-Calvin et al. 1993).

Reduced bone density is not universally reported, however. In one study of 142 men and 220 women, bone density was measured 12 years after documentation of alcohol intake by questionnaire (Holbrook and Barrett-Connor 1993). Increasing alcohol consumption was associated with higher bone density at the hip in men and in the spine in women. A small study of 19 premenopausal alcoholic women found no difference in spine, hip, or forearm bone density (Laitinen et al. 1993), but a larger cross-sectional study of postmenopausal women by this research group did observe a positive correlation between alcohol intake and bone density (Laitinen et al. 1991*c*). The Study of Osteoporotic Fractures (7,963 ambulatory, nonblack women aged 65 and older) has also found that moderate alcohol intake is associated with higher bone density (Orwoll et al. 1996). However, less than 15 percent of this cohort consumed more than one standard drink per day.

The degree to which alcohol contributes to osteopenia in the entire population is not yet known. Intriguing data at lower levels of consumption, however, suggest that more modest alcohol consumption is less likely to be associated with low bone density and may even be associated with higher bone density. Moderate alcohol intake may affect endogenous hormone levels, as discussed below, to indirectly augment skeletal mass. However, the evidence for a protective

effect of moderate alcohol consumption is not entirely compelling and should be interpreted with caution. Although the results of the epidemiologic studies were adjusted for known confounding factors, the association may not be causal, and moderate alcohol intake may merely be a marker for relative affluence (resulting in better nutrition and lifestyle during peak bone mass acquisition earlier in life). Moreover, no study of osteoporotic fracture risk in women has thus far identified any corresponding protective effect of social drinking.

Bone Histomorphometry

Epidemiologic data on alcohol and bone mass are not entirely consistent, yet studies of the cellular, hormonal, and molecular processes involved in the formation of bone have identified mechanisms by which alcohol consumption could be a determinant of bone mass. Microscopic examination of bone (bone histomorphometry) from alcoholic subjects has provided important insight into the specific nature of the skeletal disorder induced by alcohol. Adult bone mass is regulated by a remodeling cycle that is composed of an initial period of bone breakdown (resorption) by cells called osteoclasts, coupled with a proportionate amount of new bone formation by cells called osteoblasts. Skeletal remodeling is a continuous process with approximately 10 percent of bone undergoing the process at any given time. Bone formation and bone resorption rates are tightly coupled, allowing for large amounts of bone to be replaced throughout adult life without significant alterations in total bone mass.

Over the past 20 years, scientists have found in both animals and human subjects that alcohol can disrupt this cycle. Clues that this is happening include the finding that the fibrous matrix on which calcium is deposited—trabecular bone—was reduced and resorption was enhanced in rats exposed to alcohol for more than 8 weeks (Baran et al. 1980). Trabecular bone in the hip bone or femur of rats fed alcohol has also been found to be thinner, with overall mechanical strength of the bone substantially compromised compared with rats not fed alcohol (Peng et al. 1988).

Another study found that bone matrix synthesis and mineralization rates were reduced in rats fed intoxicating amounts of alcohol for 3 weeks (Turner et al. 1987).

Similar alcohol-induced histomorphometric abnormalities have been found in humans. Various studies of alcoholic patients have shown reductions in measures of bone formation and an increase in bone resorption (Schnitzler and Solomon 1984), a diminution of bone formation rates in alcoholics with no compensatory decrease in markers of resorption (Diamond et al. 1989), and a 60-percent reduction in the number of osteoblasts and a 50 percent lower mineralization rate in actively drinking alcoholics versus abstinent chronic alcoholics with no differences in resorption (Crilly et al. 1988). The overall impression from these studies seems to be that alcoholic bone disease is characterized by considerable suppression of bone formation, while indices of bone resorption, for the most part, do not differ substantially from those observed in control subjects.

The changes in bone turnover induced by alcohol can apparently be reversed by abstention. Studies have demonstrated a rapid recovery of osteoblast function, as assessed histomorphometrically and by biochemical measures of bone remodeling, within as little as 2 weeks after cessation of drinking (Diamond et al. 1989; Feitelberg et al. 1987; Laitinen et al. 1992). Moreover, a recent report suggests that bone, once lost, can be at least partially restored when alcohol abuse is discontinued (Peris et al. 1994). Hence, the bone loss in alcoholism appears to be a consequence of an imbalance in the normal tight coupling of resorption and formation, with normal resorption activity outstripping a repressed formation process. To date, no histomorphometric analyses have been performed on moderate drinkers. Such studies would be important to confirm and possibly extend the previous reports of increased bone density. The microscopic examination of skeletal tissue has the added benefit of identifying possible cellular mechanisms by which moderate alcohol intake affects bone.

Data from the 1992 National Longitudinal Alcohol Epidemiologic Survey indicate that 8.7 percent of U.S. adults consumed an average of more than two drinks a day (Dawson et al. 1995). Further, an ongoing national survey of high school students recently reported that within the past month, 24 percent of 8th graders, 40 percent of 10th graders, and 51 percent of 12th graders used alcohol (Johnston et al. 1999). The skeletal consequences of alcohol intake during adolescence, when the rapid skeletal growth ultimately responsible for achieving peak bone mass is occurring, may be especially harmful.

In a recent series of experiments, scientists have examined the effect of alcohol on the early phases of skeletal development in a model of a growing animal (Hogan et al. 1997; Sampson et al. 1996, 1997). Rats chronically exposed to alcohol from age 1 month to 3 months—a developmental period comparable to that of human adolescence and young adulthood—were compared with rats fed a diet without alcohol. Calories in the diet without alcohol were also reduced to mimic the reduction in caloric intake associated with alcohol consumption, so that any differences in bone would be due to the presence or absence of alcohol, not overall nutrition. Gross skeletal morphology—the appearance of bones on visual inspection—was not affected by alcohol, but bone density determined by calcium content in the tibial or shin bone was 25 percent lower in the alcohol-exposed animals, and whole bone strength was 40 percent lower.

These studies indicate that the adolescent skeleton is especially sensitive to the adverse effects of alcohol on bone formation. By limiting peak bone mass attainment, the development of osteoporosis later in life may be increased and its onset hastened. Adolescent alcohol consumption is frequently heavy and episodic, in "binges" (Wechsler et al. 1994). No animal studies have, as yet, examined the impact of episodic alcohol intake and compared it with continuous alcohol exposure. Furthermore, studies are needed to determine if alcohol consumption during adolescence has a lasting effect on age-related osteopenia and subsequent fracture risk.

Potential Mechanisms of Alcohol-Induced Bone Disease

Normal bone formation depends on adequate nutrition and the function and interaction of a variety of hormones and intercellular regulating factors. The effect of alcohol on the skeleton could result from a direct toxic effect on bone, or indirectly through an effect on nutritional status or hormonal regulation of bone metabolism. While the exact mechanism has yet to be established, research is providing a variety of potential pathways to alcohol-induced bone disease.

Alcohol and Nutrition

Disturbances in the ongoing balance, or homeostasis, of minerals in the body are an obvious mechanism for bone disease in alcoholics. Mild deficiencies in calcium, phosphate, and magnesium are frequently present in ambulatory alcoholics because of poor diet, malabsorption, and increased renal (kidney) excretion (Bikle et al. 1985; Kalbfleisch et al. 1963; Laitinen et al. 1992; Territo and Tanaka 1974). Yet no histomorphometric study has demonstrated any evidence of nutritional deficiency, except in patients who have previously undergone gastric surgery (Johnell et al. 1982*b*).

Vitamin D is a fat-soluble vitamin that stimulates intestinal absorption of calcium and is necessary for mineralization of new skeletal tissue. Early studies found circulating levels of the vitamin D metabolites to be low in alcoholics (De Vernejoul et al. 1983; Lalor et al. 1986; Mobarhan et al. 1984; Verbanck et al. 1977). However, subsequent investigation has excluded vitamin D deficiency as a major cause of alcohol-induced bone disease by demonstrating normal vitamin D absorption (Scott et al. 1965; Sorenson et al. 1977) and conversion to active metabolites (Posner et al. 1978) in alcoholic individuals and, more directly, by the measurement of normal free concentrations of the biologically active metabolite of vitamin D in patients with alcoholic cirrhosis and alcoholic bone disease (Bikle et al. 1984; Genant et al. 1985). These findings do not exclude the possibility of an alcohol-induced

vitamin D-resistant state, but the lack of histomorphometric evidence of osteomalacia in vitamin D-replete osteopenic alcoholic subjects (Bikle et al. 1985; Diamond et al. 1989) argues strongly against such a possibility.

Alcohol and Calciotropic Hormones

Calcitonin is a peptide produced by the thyroid gland that functions as an inhibitor of bone resorption, in effect protecting bone. In a study in which 0.8 grams per kilogram of alcohol—about 4 drinks for a 150-lb man—were administered to nonalcoholic men, plasma calcitonin levels were 38 percent higher 3 hours later (Williams et al. 1978). Alcohol-induced hypercalcitoninemia might be a mechanism for the observation that moderate intake of alcohol is associated with higher bone density, but no data exist about the duration of this effect in alcoholism.

Parathyroid hormone (PTH) is the principal regulator of blood calcium levels. The production of calcium is stimulated by a decrease in blood calcium; PTH's major actions are to increase the release of calcium from bone and reduce kidney excretion of calcium. An elevated PTH level would be a sensitive indicator of reduced circulating calcium. Most studies have failed to demonstrate a consistent effect of alcohol on PTH levels. They may be normal, reduced, or elevated in alcoholic subjects (Bikle et al. 1993; Bjorneboe et al. 1988; Johnell et al. 1982*a*). A likely explanation for the discrepant reports of PTH values is the molecular heterogeneity not only of the PTH fragments measured in the circulation, but of the radioactively labeled antibodies used in the assays for PTH. In addition, PTH is metabolized in the liver, which is frequently damaged with excessive alcohol ingestion.

Recent studies suggest that alcohol may directly interfere with PTH secretion. Scientists who administered alcohol to normal volunteers over a 3-hour period observed a marked decrease in intact PTH levels (Laitinen et al. 1991*a*). PTH levels then rebounded to above baseline after 8 hours and remained elevated for the remainder of the 16-hour study. The fall in PTH was accompanied by a fall in blood calcium and a dramatic increase in urinary calcium excretion, suggesting that the response of the parathyroid gland is impaired even in the presence of low calcium levels. It is possible that alcohol-induced changes in intracellular calcium, especially within the parathyroid gland, may explain the reduced PTH levels (Brown et al. 1995).

In subsequent studies, scientists examined the effects of more prolonged alcohol consumption and observed an increase in PTH levels accompanied by a rise in serum calcium after 3 weeks (Laitinen et al. 1991*a*). Thus, alcohol appears to have both acute and chronic effects on PTH secretion, with the net result that levels of PTH detected by immune-based assays are slightly increased. There are no reports on PTH bioactivity in the serum of alcoholic subjects to give a definitive account of the effect of long-term exposure to substantial amounts of alcohol. However, the classic signs of hyperparathyroidism are not seen on bone biopsies of affected patients (Bikle et al. 1985; Crilly et al. 1988; Diamond et al. 1989; Lindholm et al. 1991). Thus, no convincing evidence can be marshaled to support a major role for an indirect effect of alcohol on bone via alterations in calciotropic hormone levels.

Sex Hormones

Inadequate gonadal function is a well-described risk factor for osteoporosis. Alcohol abuse has been associated with sexual dysfunction in both men and women (Gavaler 1991; Van Thiel 1983; Wright et al. 1991). Men who have a long-term history of alcohol abuse often suffer from impotence, sterility, and testicular atrophy (Valimaki et al. 1982) and have reduced concentrations of plasma testosterone (Boyden and Pamenter 1983; Van Thiel et al. 1974). In women, the frequency of menstrual disturbances, spontaneous abortions, and miscarriages increases with the level of drinking, and alcohol abuse has adverse effects on fertility and sexual function, often bringing on premature menopause (Gavaler 1985; Hugues et al. 1980; Mello et al. 1993; Valimaki et al. 1984).

There is considerable interest in the question of whether consumption of alcohol at a more moderate level—one drink per day or less for women—might actually increase estrogen. Studies of both pre- and postmenopausal women have yielded mixed results (Dorgan et al. 1994; Purohit 1998; Reichman et al. 1993). In particular, recent studies suggest that alcohol increases estradiol, the most potent form of estrogen, in postmenopausal women on hormone replacement therapy, but results are inconsistent in postmenopausal women not on hormone replacement therapy (Purohit 1998).

Animal studies indicate that moderate alcohol levels increase the production of estradiol through conversion of testosterone (Chung 1990). Relative to the skeleton, studies have shown that osteoblasts possess this conversion capability (Purohit et al. 1992), thus providing a potential source for estradiol in the bone microenvironment. In addition, certain alcoholic beverages contain isoflavanoid compounds known as phytoestrogens (Gavaler 1995). These substances of plant origin are capable of binding to the estrogen receptor (Gavaler et al. 1987) and eliciting estrogen-like responses in both animals and postmenopausal women (Gavaler et al. 1991; Van Thiel et al. 1991).

Additional research is needed to clarify alcohol's effect on estrogen in postmenopausal women. If moderate alcohol consumption does result in elevated estrogen, this could be a plausible mechanism for the observations in certain epidemiologic studies that moderate drinking is associated with increased bone density. However, the level of alcohol consumption is likely to be an important factor relative to bone metabolism and other risks of alcohol consumption.

Alcohol and Bone Cells

Chronic heavy consumption of alcohol is associated with profound alterations in the growth and proliferation of a wide variety of cell types. Biochemical and histomorphometric evaluation of alcoholic subjects reveals a marked impairment in osteoblastic activity with normal osteoclastic activity. These findings argue strongly that a primary target of alcohol's adverse effects on the skeleton is the osteoblast. As bone remodeling and mineralization are dependent on osteoblasts, it follows that a deleterious effect of alcohol on these cells will ultimately lead to reduced bone mass and fractures. A number of researchers have noted that alcohol can reduce proliferation of osteoblasts. In cell culture, alcohol induced a dose-dependent reduction in cell protein and deoxyribonucleic acid (DNA) synthesis in normal human osteoblasts (Friday and Howard 1991). This reduction in proliferation has been confirmed by others studying human cells (Chavassieux et al. 1993).

Alcohol-associated reductions in cell number must stem from either overt toxicity or inhibition of intracellular signaling processes that regulate cell replication. Alcohol has been observed to enhance a process that normally leads to the preprogrammed death, or apoptosis, of particular cells (De et al. 1994; Ewald and Shao 1993).

In many cell types, alcohol-induced reductions in cell division are reversible. These reductions are associated with depletion of naturally occurring compounds called polyamines in the cell (Shibley et al. 1994). Research suggests that polyamines can regulate the synthesis of both DNA (Janne et al. 1978) and protein (Jacob et al. 1981) and may also affect the expression of genes that regulate cell division (Luscher and Eisenman 1988). Chronic exposure to alcohol results in alterations in polyamine metabolism that may contribute to the pathogenesis and progression of liver disease in alcoholic individuals (Diehl et al. 1988, 1990*a*,*b*).

In a series of experiments involving cultures of osteoblast-like bone cancer cells, alcohol impaired the induction of the first, and often rate-limiting, step in polyamine biosynthesis (Klein and Carlos 1995). This effect by alcohol was dose dependent, and it paralleled alcohol's antiproliferative effect on the cells. Addition of polyamines restored the rate of cell proliferation in the alcohol-exposed cell cultures to that observed in cultures untreated with alcohol. Additional studies failed to find any evidence for induction

of apoptosis by alcohol in these osteoblast-like cell cultures (Klein et al. 1996). The half-maximally effective concentration of alcohol to inhibit osteoblast proliferation in culture was well within the physiologic range observed in actively imbibing alcoholic subjects. A concentration of alcohol equivalent to a blood alcohol level of 0.044 percent—about half the blood alcohol level (0.08 percent) that many States define as legally intoxicated—also resulted in a substantial 20-percent decline.

These findings of a direct inhibitory effect of clinically relevant concentrations of alcohol on proliferation of these osteoblast-like cells support the histomorphometric observations of a reduced number of osteoblasts and impaired bone formation activity in humans consuming excessive amounts of alcohol (Bikle 1993; Crilly et al. 1988; De Vernejoul et al. 1983, Diamond et al. 1989; Genant et al. 1985). Furthermore, these studies indicate that impairment of cellular polyamine synthesis plays a critical role in mediating the antiproliferative effects of alcohol because the administration of externally supplied, or exogenous, polyamines overcame the inhibitory effect of alcohol on cell proliferation. Moreover, these studies suggest that alcohol must perturb some intracellular process that normally results in stimulation of the polyamine biosynthetic pathway, a vital step in osteoblast proliferation.

Further evidence implicating a direct effect of alcohol on osteoblast activity comes from studies examining the effects of alcohol on circulating osteocalcin levels. Osteocalcin is a small peptide synthesized by active osteoblasts, a portion of which is released into the circulation. Levels of osteocalcin are positively correlated with histomorphometric parameters of bone formation in healthy individuals (Garcia-Carrasco et al. 1988) and patients with metabolic bone disease (Delmas et al. 1985). Chronic alcoholic patients exhibit significantly lower osteocalcin levels than do age-matched nondrinkers (Labib et al. 1989). Moreover, alcohol exerts a dose-dependent suppressive effect on circulating osteocalcin levels (Laitinen et al. 1991*b*; Nielsen et al. 1990; Rico et al. 1987). The consumption of 50 grams of alcohol (four drinks) over 45 minutes resulted in a 30-percent decrease in serum osteocalcin levels detectable 2 hours later (Nielsen et al. 1990). Beyond these fragmentary attempts at characterization, however, little further is known about the mechanisms whereby alcohol stimulates osteoblast proliferation and growth.

Alcohol and Intracellular Signaling Processes

The subcellular mechanisms for alcohol's ability to damage any part of the body are currently not known. Researchers have suggested that alcohol may disrupt the lipids (fats) in the cell membrane and, in turn, alter the function of proteins residing in the membrane's lipid environment. Alternatively, alcohol may have a direct action on specific proteins in the membrane. There is increasing evidence that alcohol may exert significant effects on transmembrane signal transduction, a major avenue of cellular control (Hoek and Rubin 1990; Hoffman and Tabakoff 1990; Taylor 1997).

For example, a recent study found that, in an osteoblast-like cell line, alcohol can increase levels of the immune-signaling molecule, or cytokine, interleukin-6 (IL-6) (Keller et al. 1997). IL-6 contributes to the development of osteoporosis by stimulating osteoclastic activity. These findings suggest that one avenue of damage to bone from alcohol could be through an effect on IL-6.

Growth factors are signaling molecules that shape the growth and development of cells. Insulin-like growth factors I and II (IGF-I and IGF-II) are considered to be the most important local regulators of bone remodeling. Osteoblastic cells in culture can produce both IGF-I and IGF-II (Canalis et al. 1991). Molecular docking stations, or receptors, exist in the cell for IGF's. The docking of a molecule to the receptor sets off a subsequent signaling cascade within the cell that can then help dictate the nature and rate of specific cell functions. Osteoblasts are dependent on signaling via the IGF-I receptor for survival and proliferation in culture. The IGF's increase the pre-osteoblastic cell population that eventually differentiates into mature osteoblasts. Independent of their effects on cell replication, IGF's

increase collagen synthesis and matrix assembly. Through these actions it is apparent that the IGF's play a fundamental role in the maintenance of bone mass. On the basis of these findings, it is interesting to speculate that the reduced osteoblast number and bone formation that characterize alcoholic bone disease may stem entirely from a single alcohol-induced defect in intracellular signaling by the IGF receptor.

In Closing

Recent studies suggest a dose-dependent relationship between alcohol consumption and risk of fracture in both men and women. This increased risk may be, at least in part, attributable to a reduction in bone density in those with excessive alcohol intake. Alcoholic bone disease is characterized by impaired bone formation in the face of relatively normal bone resorption. The uncoupling of these two physiologic processes results in defective remodeling of skeletal tissue and, in turn, reduced bone mass and increased fracture risk. The growing skeleton may be especially sensitive to the adverse effects of alcohol. Experiments using well-defined osteoblastic model systems indicate that the observed reductions in bone formation result from a direct, antiproliferative effect of alcohol on the osteoblast itself. Further studies are necessary to establish the underlying mechanisms by which alcohol exerts its antiproliferative effects on the osteoblast. At present, sustained reduction in alcohol intake is the only effective therapy for alcohol-induced bone disease. An improved understanding of the pathogenesis of alcohol-induced bone disease may lead to alternative therapeutic avenues.

Because of the potential impact on a large proportion of our society, of considerable interest is the provocative finding of increased bone density in social drinkers with more moderate alcohol consumption. Whether this increase in bone density can be ascribed to direct stimulatory effects of alcohol on estrogen or calcitonin levels, or both, or to concomitant lifestyle and socioeconomic factors has yet to be adequately explored. Specific studies are needed to address the question of whether moderate alcohol consumption is a protective factor against fracture, and if so, at what level the skeletal advantages of alcohol intake are obviated by the increased risks from alcohol excess.

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